REMARKS

Claims 25-28 are currently pending. Claim 25 has been amended.

In particular, claim 25 has been amended to specify that the autocrine growth factor specific for a tumor cell is coupled, *e.g.*, chemically or recombinantly coupled, to the antibody or antigen binding fragment. Support for this amendment to claim 25 can be found throughout the specification, for example, at page 6, lines 26-30.

No new matter has been added. The foregoing amendments should in no way be construed as an acquiescence to any of the Examiner's rejections, and have been made solely to expedite the prosecution of the application. Applicants reserve the right to pursue the claims as originally filed in this or a separate application(s).

Rejection of Claims 25-27 Under 35 U.S.C. § 112, First Paragraph

The Examiner has rejected claims 25-27 under 35 U.S.C. § 112, first paragraph, for failing to comply with the written description requirement. Specifically, the Examiner states that:

> [t]he written description in this case has only set forth a bispecific molecule comprising an FcγRI antibody or antigen binding fragment thereof that is not inhibited by endogenous Ig and a bombesin or gastrin-releasing peptide (GRP), and is therefore not commensurate in scope to claims that read on the said FcγRI antibody or antigen binding fragment and any and all autocrine growth factors.

The Examiner further states that:

> Applicant does not appear to have reduced to practice a representative number of autocrine growth factors so as to be entitled to the genus of all autocrine growth factors claimed. Neither has Applicant provided sufficient written description of any structure that may be correlated from the structure of bombesin or GRP provided to encompass all growth factors. Autocrine growth factors encompass many different molecules with highly diverse structures and biologically diverse functions. Thus the genus of compounds encompassed by this term is extensive and the artisan would not be able to recognize that Applicant was in possession of the invention as now claimed.

Applicants respectfully traverse this rejection. According to the Written Description Guidelines:

> [w]hat constitutes a "representative number" is an inverse function of the skill and knowledge in the art. Satisfactory disclosure of a "representative number" depends on whether one of skill in the art would recognize that the applicant was in possession of the necessary common attributes or features of the elements possessed by the members of the genus in view of the species disclosed . . .

(Federal Register (Friday, January 5, 2001) Vol.66(4) at page 1106, third column).

In the present case, the common attributes or features possessed by the members of the claimed genus include the feature of being recognized as an autocrine growth factor and, thus, being capable of binding to the same cell which expresses the factor, *i.e.*, a tumor cell as specified in the pending claims. As was well known in the art at the time of the present invention, autocrine growth factors (AGFs) are soluble factors which are secreted by a cell and which bind to receptors that are expressed on the same cell, thus, creating an autogenous loop in which a product (*i.e.*, the AGF) acts back on the cell that produces it, *e.g.*, to create a mechanism of growth control. As was known in the art, such AGFs, *e.g.*, AGFS which are secreted and which bind to tumor cells, do not always share structural elements and can include molecules as diverse as EGF and epiregulin. However, despite their different structural characteristics, these molecules are recognized as sharing the functional characteristics of AGFs as defined above.

Further, Applicants teach several specific examples of the claimed AGFs in the present specification. These include target cell specific ligands that bind to tumor cell receptors, such as bombesin, gastrin releasing peptide (GRP), and functional fragments or analogues thereof.

Accordingly, in view of the fact that the relevant identifying characteristics common to the genus of autocrine growth factors were known in the art, combined with the particular examples described in Applicants' specification, one of ordinary skill in the art would recognize that Applicants were in possession of the claimed invention at the time of filing. In fact, based on the Examiner's statement at page 3 of the previous Office Action (mailed February 10, 2003 as Paper No. 9), it appears that the Examiner agrees that a skilled artisan would be able to identify the claimed genus since the Examiner stated that "it is routine for one of skill in the art to conjugate any growth factor to any antibody or antigen binding fragment . . ."

Based on at least the foregoing, the present application meets the written description requirement for the invention as claimed. Accordingly, Applicants respectfully request the Examiner to reconsider and withdraw the rejection of claims 25-27 under 35 U.S.C. §112, first paragraph.

Rejection of Claim 25 Under 35 U.S.C. § 102(b)

Claim 25 is rejected as being anticipated by Ball *et al.* (1992) J. Hematother 1(1):85-94. In particular, the Examiner states that:

> Ball *et al.* teach a bispecific molecule comprising an autocrine growth factor for a tumor cell and an antibody or antigen binding fragment thereof which binds to FcγRI on an effector cell at a site that is not inhibited by endogenous immunoglobulin. Specifically, "monocytes plus BsAb plus human serum resulted in maximal killing (50-80%)" of promyelocytic leukemia cells.

Based on this, the Examiner concludes that "absent evidence to the contrary, the addition of human serum would inherently comprise an autocrine growth factor specific for a tumor cell."

Applicants respectfully traverse this rejection. The pending claims are drawn to a bispecific molecule comprising an autocrine growth factor specific for a tumor cell coupled to an antibody, or antigen binding fragment thereof, which binds to FcγRI on an effector cell at a site that is not inhibited by endogenous immunoglobulin. Ball *et al.* fail to teach or suggest conjugating an autocrine growth factor to any type of molecule, let alone the concept of using a non-immunoglobulin molecule, such as an autocrine growth factor, to target a tumor cell, as encompassed by the claims. Ball *et al.* describe immunotherapy of CD15-bearing tumors using a bispecific antibody comprising an anti-CD15 binding region and anti-CD64 binding region. Accordingly, Ball *et al.* fail to teach or suggest the claimed bispecific molecule which includes an autocrine growth factor specific for a tumor cell coupled to an anti-FcγRI antibody. Therefore, the claims are novel in view of Ball *et al.*

Rejection of Claims 25-28 Under 35 U.S.C. § 103(a)

Claims 25-28 are rejected as being unpatentable over of Ball *et al.* (1992) in view of Cuttita *et al.* (1985) Nature 316(6031):823-826. Specifically, the Examiner states that "Ball *et al.* disclose the production of a bispecific molecule using an anti-FcγRI antibody that is able to bind to FcγRI outside of the Ig binding site conjugated to another molecule that has the ultimate purpose of associating with a tumor cell." The Examiner admits that "Ball *et al.* do not specifically characterize that the bispecific molecule is able to bind to GRP receptors on small cell lung carcinoma cells nor does it teach the specific autocrine growth factor, namely bombesin or GRP." However, the Examiner further states that "this deficiency is made up by Cuttita *et al.* wherein it is disclosed that bombesin and bombesin like peptides specifically bind to cellular receptors on SLC cells."

From this, the Examiner concludes that "it would have been *prima facie* obvious to one of ordinary skill at the time the invention was made to manufacture a bispecific molecule comprising an anti-FcγRI antibody or antigen binding fragment thereof and bombesin or GRP autocrine growth factor in order to target SCLC cells."

Applicants respectfully traverse this rejection. As described above, claim 25 is directed to a bispecific molecule comprising an autocrine growth factor specific for a tumor cell coupled to an anti-FcγRI antibody, or antigen binding portion thereof. The autocrine growth factor functions within the claimed bispecific molecule to bind the target tumor cell and the anti-FcγRI antibody functions to bind an effector cell, thus, bringing the two cells together to initiate effector cell-mediated cell killing, such as ADCC or complement mediated cell death. Dependent claims 26-28 further specify that the tumor cell is a human small-cell lung carcinoma cell; the autocrine growth factor binds to the gastrin-releasing peptide receptor of the human small-cell lung carcinoma cell; and the autocrine growth factor is selected from the group consisting of bombesin and gastrin-releasing peptide and gastrin releasing peptide receptor binding analogues thereof.

It would not have been obvious to have combined the teachings of Ball *et al.* and Cuttita *et al.* for at least the following reasons. As discussed above, Ball *et al.* describe immunotherapy of CD15-bearing tumors using a bispecific antibody comprising an anti-CD15 binding region and anti-CD64 binding region. Ball *et al.* fail to teach or suggest the claimed bispecific molecule which includes an autocrine growth factor specific for a tumor cell, *i.e.*, a non-immunoglobulin tumor ligand, coupled to a anti-FcγRI antibody.

Cuttita *et al.* fail to make up for the deficiencies of Ball *et al.* Cuttita *et al.* merely teach that bombesin and bombesin-like peptides (BLPs), such as GRP, can function as autocrine growth factors in human small-cell lung cancer. Specifically, Cuttita *et al.* describe the use of anti-bombesin antibodies which successfully bind to the C-terminal region of BLPs and block the binding of BLPs to cellular receptors, thus, inhibiting the clonal growth of the cells.

Accordingly, Cuttita *et al.* do not in any manner suggest the use of a tumor ligand to target a tumor cell. Instead, Cuttita *et al.* describe the use of antibodies which bind to and inhibit tumor ligands. Thus, even if one were to combine the teachings of Ball *et al.* and Cuttita *et al.*, the result would be a bispecific molecule comprising an anti-BLP antibody joined to an anti-FcγRI antibody. Such a bispecific molecule would not bind to the same targets as the claimed bispecific molecule, nor would it function in the same way. Applicants were the first to show

that ligands specific for a particular target cell can be useful for initiating a specific antibody-dependent effector cell-mediated cytotoxicity against the target cell (ADCC).

Therefore, based at least on the foregoing, one of ordinary skill would not have been motivated to combine the teachings of the cited references since neither reference, either alone or in combination, teaches or suggests conjugating a tumor ligand to any antibody, let alone the claimed anti-FcγRI antibodies. Further, the two references are concerned with targeting entirely different molecules; *i.e.*, one is concerned with using a bispecific molecule to target CD15-bearing cells and FcR-bearing cells, while the other is concerned with using a monospecific antibody to target BLPs. Accordingly, there is no nexus or connection whatsoever that would have motivated one of ordinary skill in the art to have combined the cited references in the manner suggested by the Examiner. Moreover, even if they had combined these references, they would not have arrived at the claimed invention since neither reference teaches the use of an autocrine growth factor to target a tumor cell, as claimed.

Accordingly, for at least the foregoing reasons, Applicants respectfully request reconsideration and withdrawal of the rejection of claims 25-28 under 35 U.S.C. § 103(a).

CONCLUSION

Applicants respectfully submit that the application is now in condition for allowance. If a telephone conversation with Applicants' Attorney would expedite the prosecution of the above-identified application, the examiner is urged to call Applicants' Attorney at (617) 227-7400.

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Respectfully submitted,

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